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(57) Abstract

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising certain amino acid salts of propionic acid non-steriodal anti-inflammatory agents along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine and (d) an antitussive.

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COMPOSITIONS CONTAINING AN AMINO ACID SALT OF PROPIONIC ACID NON-STEROIDAL ANTIINFLAMMATORY AGENT AND AT LEAST ONE OF A DECONGESTANT, AN EXPECTORANT, AN ANTIHISTAMINE AND AN ANTITUSSIVE

TECHNICAL FIELD

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising certain amino acid salts of propionic acid non-steriodal anti-inflammatory agents along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine, and (d) an antitussive.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying infliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

Early symptoms may be minimal with only mild malaise, sore throat and nasal complaints. With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of illness and progress to maximum severity by the second or third day. Along with nasal symptoms may come sore, dry or scratchy throat and hoarseness and cough. Other symptoms may include mild burning of the eyes, loss of smell and taste, a feeling of pressure or fullness in the sinuses or ears, headache, and vocal impairment. Fever can occur, but is uncommon. Influenza infection generally includes fever, often of sudden onset and persisting for several days, and with great severity; generalized aches and pains; fatigue and weakness; and chest discomfort.

At present, only symptomatic treatment is available for the common cold. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect costs, based on the amount of loss in wages because of restricted activity are substantially higher.

Exemplary prior art formulations for treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

The use of non-steroidal anti-inflammatory drugs to combat inflammation and attendant pain is accepted medical practice. The non-steroidals are commonly employed to relieve pain and inflammation associated with, for example, bursitis, arthritis, headache and the like. Among the most commonly used drugs of the non-narcotic analgesic class of drugs are aspirin, acetaminophen, ibuprofen and naproxen. Aspirin, acetaminophen and ibuprofen have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multi--symptom alleviating compositions. These commercially marketed products generally contain in addition to aspirin, acetaminophen or ibuprofen, one or more antihistaminics, decongestants, cough-suppressants, antitussives and expectorants.

The ornithine, lysine and arginine salts of ibuprofen useful for providing relief from pain and inflammation have been disclosed in, for example, U.S. 4,279,926 to Bruzzese et al., issued July 21, 1981. A process for the preparation of ibuprofen lysine tablets has been disclosed in EP 505,180, published March 19, 1992. The use of the S(+) form of ibuprofen has been disclosed in, for example, U.S. Patent 4,851,444 to Sunshine et al. issued July 25, 1989 and in combination with antihistamines in WO 9,205,783 to Gates et al. published April 16, 1992.

The use of naproxen as well as other of the newer non-steroidal anti-inflammatory agents (i.e., excluding aspirin, acetaminophen and phenacetin) in the preparation of cough/cold pharmaceutical compositions has been disclosed in, for example, U.S. Patent 4,552,899 to Sunshine et al. issued November 12, 1985. The use of some of these newer NSAID's alone to treat upper respiratory infections has been disclosed in "Therapeutic Utility of Naproxen in Acute Upper Respiratory Infection -- Multiclinical Double Blind Study" Kansenshogaku Zasshi 52 (5):148--163 (1978), "Clinical Evaluation of Sulindac (Clinoril®) in the Treatment of Acute Upper Respiratory Tract Inflammation -- Double Blind Comparison With Ibuprofen", Kansenshogaku Zasshi, Vol. 57, No. 3, pp. 260-272 (1983); "Double Blind Controlled Study of Miroprofen in Acute Upper Respiratory Tract Infections. Comparison with Ibuprofen" Kansenshogaku Zasshi, Vol. 50, No. 5, pp. 435-453, 1982, "Therapeutic Effects of Fenbufen on the Common Cold. Multiclinic Double--Blind Study" Kansenshogaku Zasshi, Vol. 51, No. 4, pp. 184-196, (1977); "Clinical Evaluation of Clinoril Tablets in Acute Respiratory Tract Infections", Kansenshogaku Zasshi, Vol. 56, No. 12, pp. 1186-1195, 1982.

The present inventors have found that selected compositions comprising certain amino acid salts of the propionic acid NSAIDs with at least one of (a) a decongestant, (b) an expectorant (c) and antihistamine, and (d) an antitussive provides improved treatment, management or mitigation of cold, cold-like and/or flu symptoms.

It is therefore an object of the present invention to provide a method for the treatment of cough, cold, cold-like and/or flu symptoms in a mammalian organism in need of such treatment comprising administering to such organism the compositions of the present invention. Such symptoms as used herein refer to coryza, nasal congestion, sinus congestion, sinus pain, upper respiratory infections, allergic rhinitis, otitis, sinitis, etc.

SUMMARY OF THE INVENTION

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising an amino acid salt of a propionic acid NSAID along with at least one of (a) a decongestant, (b) an expectorant, (c) an antihistamine and (d) an antitussive.

All percentages and ratios used herein are by weight unless otherwise indicated.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compositions and methods for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising an amino acid salt of a propionic acid NSAID along with at least one of (a) a decongestant, (b) an expectorant (c) an antihistamine and (d) an antitussive.

The term "amino acid salt" refers to salts derived from pharmaceutically acceptable organic non-toxic bases of primary, secondary, tertiary and quaternary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, ornithine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purines, piperazine, piperidine, polyamine resins and the like.

The propionic acid derivatives of the non-steroidal anti-inflammatory agents which are useful in the compositions of the present invention are well-known to those skilled in the art and are disclosed in, for example, U.S. Patent 4,552,899 to Sunshine et al., issued November 12, 1985, incorporated by reference herein. For

detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974), both of which are incorporated by reference herein.

The preferred non-steroidal anti-inflammatory agents useful in the composition of the present invention include the amino acid salts of the propionic acid derivatives such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic. Mixtures of these non-steroidal anti-inflammatory agents may also be employed. Of these propionic acid NSAIDs, ibuprofen, naproxen and ketoprofen are most preferred.

Most preferred for use herein is the S(+) isomer of these NSAID salts. The term "S(+)" as applied to the analgesic agents herein is intended to encompass the dextrorotatory or S(+) isomer of the amino acid salt derivatives thereof. The expression "substantially free of the R(-) antipode" as used in conjunction with the term "S(+)" means that the S(+) enantiomer is sufficiently free it is R(-) antipode to exert the desired onset-hastened and enhanced analgesic effect. Practically speaking, this means that the active ingredient should contain at least 90% by weight of the S(+) enantiomer and 10% or less weight R(-) enantiomer. Preferably, the weight ratio of S(+) enantiomer to R(-) enantiomer is greater than 20:1, more preferably greater than 97:3. Most preferably the S(+) enantiomer is 99 or more % by weight free of R(-) enantiomer, i.e., the weight ratio of S to R is approximately equal to or greater than 99:1.

The safe and effective amount of the amino acid salts of ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic generally ranges from about 7.5 mg to about 1000mg, and are generally the same as their acid derivatives counterparts. Useful dosage of these agents can be found in The Physicians' Desk Reference, 47th Edition (1993) and in U.S. Patent 4,552,899 to Sunshine et al., issued November 12, 1985, both of which are incorporated by reference herein.

For example, the safe and effective amount of the amino acid salt of ibuprofen used in the compositions of the present invention generally ranges from about 50 to about 800 mg, preferably from about 50 to about 400 mg, more preferably from about 50 to about 200 mg and most preferably from about 50 to

about 100 mg. The safe and effective amount of the amino acid salt of flurbiprofen used in the compositions of the present invention generally ranges from about 12.5 to about 300 mg, preferably from about 12.5 to about 200 mg, more preferably from about 12.5 to about 100 mg and most preferably from about 12.5 to about 50 mg. The safe and effective amount of the amino acid salt of ketoprofen used in the compositions of the present invention generally ranges from about 5 to about 100 mg, preferably from about 5 to about 75 mg, more preferably from about 5 to about 50 mg and most preferably from about 5 to about 25 mg. Generally, the amount of the S(+) isomers of these agents will be about half of the amount of the racemic mixture.

The compositions of the present invention also include at least one other pharmacological active selected from the following class: (a) a decongestant, (b) an expectorant (c) an antihistamine and (d) an antitussive. The decongestants useful in the compositions of the present invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof. The antitussives useful in the present invention include those such as dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts, and mixtures thereof. The antihistamines useful in the present invention include those such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbromphreniramine, triprolidine, azatadine, doxylamine, tripelennamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and terfenadine, their pharmaceutically acceptable salts and mixtures thereof. The expectorants (also known as mucolytic agents) useful in the present invention include glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts, and mixtures thereof. All of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

Preferably, the pharmaceutical compositions of the present invention comprise the analgesic agent and other pharmacological active in a ratio of anal-

gesic agent:pharmacological active of from about 200:1 to about 1:1, preferably from about 50:1 to about 1:1 and most preferably from about 10:1 to about 1:1.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, lozenges and bulk powders and liquid forms such as syrups and suspensions. These oral forms comprise a safe and effective amount, usually at least about 5% of the active component. Solid oral dosage forms preferably contain from about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95% of the active component. Liquid oral dosage forms preferably contain from about 1% to about 50% and more preferably from about 1% to about 25% and most preferably from about 3% to about 10% of the active component.

Tablets can be compressed, triturated, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. Also useful are soft gelatin capsules.

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, taste-masking agents, coloring agents, and flavoring agents. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

In preparing the liquid oral dosage forms, the active component is incorporated into an aqueous-based orally acceptable pharmaceutical carrier consistent with conventional pharmaceutical practices. An "aqueous-based orally acceptable pharmaceutical carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension of the pharmaceutical composition in an aqueous vehicle containing a suitable suspending agent. Suitable suspending agents include

Avicel RC-591 (a microcrystalline-cellulose/sodium carboxymethyl cellulose mixture available from FMC), guar gum and the like. Such suspending agents are well known to those skilled in the art. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the active component and other optional non-active ingredients, the total water content, based on the weight of the final composition, will generally range from about 20 to about 75%, and, preferably, from about 20 to about 40%, by weight/volume.

Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from about 5 to about 25 volume/volume percent and, most preferably, from about 10 to about 20 volume/ volume percent, of the co-solvent.

The compositions of this invention may optionally contain one or more other known therapeutic agents, particularly those commonly utilized in cough/cold preparations, such as, for example, a s bronchodilator such as terbutaline, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline and albuterol as well as other analgesic agents such as acetaminophen and aspirin. A highly preferred optional component is caffeine. Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate, to prolong and enhance shelf life.

METHOD OF TREATMENT

The amount of the pharmaceutical composition administered depends upon the percent of active ingredients within its formula, which is a function of the amount of the naphthalene derivative and any optional components such as a decongestant, cough suppressant, expectorant and/or antihistamine required per dose, stability, release characteristics and other pharmaceutical parameters.

Usually from about 1 mg/kg to about 50 mg/kg per day, preferably from about 2 mg/kg to about 30 mg/kg per day and most preferably from about 3 mg/kg per day to about 20 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose, or,

preferably, in multiple (two to six) doses repeatedly or sustained release dosages over the course of treatment. Generally, each individual dosage of the pharmaceutical compositions of the present invention range from about 1 mg/kg to about 25 mg/kg, preferably from about 2 mg/kg to about 15 mg/kg and most preferably from about 3 mg/kg to about 10 mg/kg. While dosages higher than the foregoing are effective to provide relief from cough, cold-like, flu and flu-like symptoms, care must be taken, as with any drug, in some individuals to prevent adverse side effects.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

EXAMPLE I

A hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
Ibuprofen Lysinate	200 mg
Pseudoephedrine HCl	30 mg

Triturate active ingredients and q.s. with lactose to selected capsule size.

Administration of 1 or 2 of the above capsules to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

EXAMPLE II

A hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

Ingredient	Amount
Naproxen Lysinate	200 mg
Pseudoephedrine HCl	30 mg
Astemizole	5 mg
Glyceryl guaiacolate	100 mg

Triturate active ingredients and q.s. with lactose to selected capsule size.

Administration of 1 or 2 of the above capsules to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

EXAMPLE III

A liquid composition for oral administration is prepared by combining the following ingredients:

Ingredient	% W/V
Ketoprofen Lysinate	1.00
Alcohol (95%)	25.000
Pseudoephedrine HCl	0.30

Propylene Glycol	25.000
Sodium Citrate	2.000
Citric Acid	0.250
Liquid Sugar (Simple Syrup)	25.000
Glycerin	7.000
Colorants	0.008
Flavor	0.500
Water, Purified QS	100.000

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, and actives other than ibuprofen are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then colorants added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the ketoprofen lysinate is added to the alcohol while stirring. The propylene glycol, other actives and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 teaspoonsful) to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

EXAMPLE IV

A liquid composition for oral administration is prepared by combining the following ingredients:

Ingredient	% W/V
Ibuprofen Argininate	1.00
Chlorpheniramine Maleate	0.02
Pseudoephedrine HCl	0.30
Alcohol (95%)	25.00
Propylene Glycol	25.00
Sodium Citrate	2.00
Citric Acid	0.25
Liquid Sugar (Simple Syrup)	25.00
Glycerin	7.00
Colorants	0.008
Flavor	0.50
Water, Purified QS	100.00

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, pseudoephedrine HCl and chlorpheniramine maleate are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the ibuprofen argininate is added to the alcohol while stirring. The propylene glycol and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 Teaspoonsful) to a human in need of treatment provides improved analgesic and/or anti-inflammatory effect.

EXAMPLE V

A liquid composition for oral administration is prepared by combining the following ingredients:

Ingredient	% W/V
S(+) Ibuprofen Lysinate	1.00
Pseudoephedrine HCl	0.30
Chlorpheniramine Maleate	0.02
Dextromethorphan HBr	0.15
Alcohol (95%)	25.00
Propylene Glycol	25.00
Sodium Citrate	2.00
Citric Acid	0.25
Liquid Sugar (Simple Syrup)	25.00
Glycerin	7.00
Colorants	0.008
Flavor	0.50
Water, Purified QS	100.00

The purified water (approximately 10% of the final batch volume) is poured into a batch container equipped with a lightnin' mixer. The sodium citrate, citric acid, pseudoephedrine HCl and chlorpheniramine maleate are added sequentially and dissolved with agitation. The glycerin and liquid sugar are then added. In a separate container the colorants are added to purified water (approximately 0.5% of the final batch volume). This colorant solution is then added to the first batch container. In a separate container the S (+) ibuprofen lysinate and dextromethorphan HBr are added sequentially to the alcohol while stirring.

The propylene glycol and flavors are added to this alcohol premix and the resulting mixture is stirred until homogeneous and then added to the first container. The remaining purified water is added to the resulting mixture and stirred.

Administration of 10 ml to 20 ml (2 to 4 teaspoonful) to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

What is Claimed is:

1. A composition for providing improved treatment, management or mitigation of cold, cold-like and/or flu symptoms by administering a safe and effective amount of a composition comprising an amino acid salt of a propionic acid nonsteroidal anti-inflammatory agent along with at least one of (a) a decongestant, (b) an expectorant, (c) an antitussive and (d) an antitussive.

2. A pharmaceutical composition according to Claim 1 wherein said propionic acid derivative is selected from the group consisting of ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofen, preferably wherein said propionic acid derivative is selected from the group consisting of ibuprofen, naproxen, flurbiprofen, and ketoprofen and wherein said amino acid salt is selected from the group consisting of triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, ornithine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purine, piperazine and piperidine and mixtures thereof.

3. A pharmaceutical composition according to any of the preceding Claims wherein: said decongestant is pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, mixtures thereof or pharmaceutically acceptable salts thereof; wherein said antitussive is selected from the group consisting of dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, mixtures thereof or pharmaceutically acceptable salts thereof; wherein said expectorant is an expectorant or mucolytic such as glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine, bromhexine and ambroxol, mixtures thereof or pharmaceutically acceptable salts thereof; and wherein said antihistamine is selected from the group consisting of chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbromphreniramine, triprolidine, doxylamine, tripelennamine, cyproheptadine, carbinoxamine, bromodiphenhydramine, pyrilamine, acrivastine, AHR-11325,

phenindamine, astemizole, azatadine, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and terfenadine, mixtures thereof or pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition according to any of the preceding Claims which comprises the S(+) enantiomer of the amino acid salt of a propionic acid nonsteroidal anti-inflammatory agent.

5. A pharmaceutical composition according to any of the preceding Claims comprising from 5 to 50 mg S(+)-ketoprofen lysinate.

6. A pharmaceutical composition according to any of Claims 1 through 4 comprising from 50 to 800 mg S(+)-ibuprofen lysinate.

7. A pharmaceutical composition according to any of Claims 1 through 4 comprising from 50 to 800 mg S(+)-naproxen lysinate.

8. A method for the treatment of cough, cold, cold-like and/or flu symptoms in a mammalian organism in need of such treatment comprising administering to such organism the composition of any of the preceding Claims.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/09581

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/19 A61K31/445 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 17171 (MERCK & CO., INC.) 15 October 1992 see claims see page 4, line 22-26	1-4,6,8
X	WO,A,92 17177 (MERCK & CO., INC.) 15 October 1992 see abstract see page 4, line 24-28	1-4,6,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 1994	20. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	LEHERTE, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09581

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claim 8 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US 94/09581

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9217171	15-10-92	AU-A-	1766292	02-11-92
		CA-A-	2107331	02-10-92
		EP-A-	0577757	12-01-94
		JP-T-	6506684	28-07-94
WO-A-9217177	15-10-92	US-A-	5164398	17-11-92
		CA-A-	2107332	02-10-92
		EP-A-	0577772	12-01-94
		JP-T-	6506472	21-07-94